2,2,2-Trifluoroethyl 2-bromophenyl thioether **3** [X = S, $R^1$ = Br, $R^2$ = H; bp 64–65 °C (0.05 mm)] was used as the starting compound in the sulfur series. It was synthesized in the same way as the oxygen analogue noted above, and on treatment with 4 equiv of an alkyl- or aryllithium ($R^3$Li) in ether, gave, after quenching, without event, the thianaphthene[5] **6** or **7** (X = S). The lower yields in the benzofuran and thianaphthene series are probably due to competitive nucleophilic attack of the lithium reagent on the intermediate acetylenes to displace[4,6] phenoxide or thiophenoxide, respectively.

In the nitrogen series we used *N*-(2,2,2-trifluoroethyl)-*N*-methyl-*m*-anisidine **3** (X = $NCH_3$, $R^1$ = H, $R^2$ = $OCH_3$) as a model compound. This nonvolatile oil was synthesized[7] by reduction of *N*-(trifluoroacetyl)-*N*-methyl-*m*-anisidine with diborane and on treatment with 4 equiv of an alkyllithium ($R^3$Li), followed by quenching with $H^+$ or E (Scheme II), was cleanly converted to the substituted indoles **6** or **7** (X = $NCH_3$, $R^2$ = $OCH_3$).

Table I not only indicates the scope of the reaction but also demonstrates the potential for heterocyclic ring formation by this new intramolecular carbanionic addition to acetylenes.

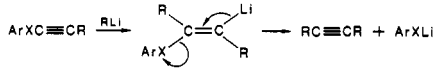
The following preparation of the substituted indole **7d** illustrates the general experimental procedure: To a solution of *N*-(2,2,2-trifluoroethyl)-*N*-methyl-*m*-anisidine **3** (0.219 g, 1 mmol) in dry THF, under an atmosphere of nitrogen at −78 °C, was added *n*-BuLi (2 mL; 4 equiv; 2 M in hexane). The reaction was warmed to room temperature gradually over 4–6 h; after the mixture was cooled to 0 °C, 0.2 mL of 1,2-epoxy butane was added, and the mixture was stirred for 1 h. Aqueous workup and isolation of the product by dichloromethane extraction, followed by silica gel chromatography (8:2 hexane/ethyl acetate) gave indole **7d** as a pale yellow solid (0.170 g; 60%; mp 94–95 °C).

Alternate routes to the intermediate acetylenic compounds related to **4**, which should permit greater flexibility in the substitution pattern, are being explored. Attempts to utilize this general methodology for the synthesis of other heterocyclic ring systems are in progress.

**Acknowledgment.** We acknowledge the receipt of an H.H.S/NIH grant (AI19709) for the partial support of this work.

**Registry No.** **3** (X = O, $R^1$ = $R^2$ = H), 17351-95-0; **3** (X = S, $R^1$ = Br, $R^2$ = H), 105230-43-1; **3** (X = NMe, $R^1$ = H, $R^2$ = OMe), 60036-83-1; **6a**, 36724-27-3; **6b**, 105230-34-0; **6c**, 36724-25-1; **6d**, 105230-36-2; **6e**, 105230-37-3; **6f**, 14315-12-9; **6g**, 105230-39-5; **6h**, 105230-40-8; **7a**, 105230-35-1; **7b**, 105230-38-4; **7c**, 105230-41-9; **7d**, 105230-42-0; *N*-(trifluoroacetyl)-*N*-methyl-*m*-anisidine, 32368-27-7.

(6) It is known[4] for example that when 1-phenoxy-2-phenylacetylene is treated with phenyllithium only diphenyl acetylene is formed. A possible mechanism for the formation of these disubstituted acetylenic by products is noted below. This would be analogous to anionic additions




observed with 1-chloro-2-phenylacetylene (Kende, A. S.; Fludzinski, P.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551) with the ArX group behaving as a pseudohalogen in our cases. However addition, at an earlier point during the dehalogenation process, cannot be ruled out.

(7) *N*-Methyl-*N*-(trifluoroacetyl)-*m*-anisidine (3.5 g, 1.5 mmol) and 30 mL of diborane (30 mmol, 1 M solution in THF) was heated under reflux under an atmosphere of nitrogen for 16 h. Normal workup followed by silica gel chromatography (9:1 hexane/ethyl acetate) gave 2.95 g (90%) of compound **3** (X = $NCH_3$, $R^1$ = H, $R^2$ = $OCH_3$).

(8) Satisfactory analytical and physical data were obtained for all new compounds reported.

(9) Ether rather than THF was used as the solvent in the cases of the thioethers.

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## Allylic Stereocenter Directed Asymmetric Conjugate Addition. Enantioselective Synthesis of 3-Alkylsuccinaldehydic Acid Methyl Esters

*Summary:* Cuprate reagents add to ester **2** with excellent $\pi$-face selectivity (≥95:5) and furnish the title compounds in high enantiomeric excess after removal of the chiral auxiliary.

*Sir:* Asymmetric conjugate addition to $\alpha,\beta$-unsaturated carbonyl compounds has been receiving considerable attention.[1,2] In particular the problem of additions to conjugated olefins bearing an allylic stereocenter has been considered from both a theoretical and experimental point of view.[2]

As a part of our study regarding $\pi$-face differentiation induced by a norephedrine-derived oxazolidine,[3] we examined conjugate addition to unsaturated ester **2**. We found that cuprate reagents add to **2** with excellent (≥95:5) diastereoselectivity to give in good yield esters **3a–f** (Scheme I, Table I).[4] Adducts **3** were in turn transformed into aldehydes **4a–d** of known absolute configuration[5,6] (Table II) by a two-step procedure (note *a*, Table II[7]) that allows the recovering of the intact chiral auxiliary.

Since both enantiomeric forms of norephedrine are commercially available this method allows the synthesis

(1) Tomioka, K.; Koga, K. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, p 201. Posner, G. H. *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 2, p 225. Lutomsky, K. A.; Meyers, A. I. *Asymmetric Synthesis*; Academic: New York, 1984; Vol. 3, p 213. Leading references: Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212. Soai, K.; Machida, H.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1985**, 469. Tomioka, K.; Sudani, M.; Shinmi, Y.; Koga, K. *Chem. Lett.* **1985**, 329. Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, 4967. Leyendecker, F.; Laucher, D. *Ibid.* **1983**, 3517. Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, 369. Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019. Heathcock, C. H.; Oare, D. A. *Ibid.* **1985**, *50*, 3022. Heathcock, C. H.; Norman, M. H., Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.

(2) (a) Trost, B. M.; Lynch, J.; Renaut, P. *Tetrahedron Lett.* **1985**, 6313 and references therein. (b) Roush, R. H.; Lesur, M. B. *Ibid.* **1983**, 2231 and references therein. (c) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. Heathcock, C. H.; Uehling, D. E. *J. Org. Chem.* **1986**, *51*, 279. (d) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, 6015.

(3) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C.; DeMunari, S. *Tetrahedron Lett.* **1985**, 5459.

(4) Chiral oxazolidines derived from ephedrine have been used as 1,3-asymmetric inductors in cuprate additions to unactivated double bonds for the stereoselective synthesis of $\beta$-alkyl aldehydes with fairly good results: Hucke, M.; Auboult, J.; Pourcelot, G.; Berlan, J. *Tetrahedron Lett.* **1983**, 585. Mongeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1984**, *40*, 1803. Berlan, J.; Besace, J.; Stephan, E.; Cressan, P. *Tetrahedron Lett.* **1985**, 5765.

(5) Asymmetric synthesis of 3-alkylsuccinaldehydic acid methyl esters was described by Mukaiyama: Asami, M.; Mukayiama, T. *Chem. Lett.* **1979**, 569.

(6) **3e** and **3f** were reduced respectively to **3c** and **3d** (5% Rh–alumina, $H_2$), before removing the chiral auxiliary.

(7) Under the conditions here described **3e** underwent double bond migration to give the more stable $\alpha,\beta$-unsaturated aldehyde.

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**Table I. Cuprate Addition to 2[a]**

| entry | cuprate reagent | temp | product | diast[b] ratio | config[c] | yield, % |
|---|---|---|---|---|---|---|
| 1 | $Me_2CuLi$ | −25 °C | **3a** | ≥95:5 | *S* | 70 |
| 2 | $Me_2CuLi/Me_3SiCl$[d] | −78 °C | **3a** | ≥95:5 | *S* | 72 |
| 3 | $Bu_2CuLi$ | −25 °C | **3b** | ≥95:5 | *S* | 70 |
| 4 | $Et_2CuLi$ | −25 °C | **3c** | ≥95:5 | *S* | 70 |
| 5 | $(H_2C{=}CH)_2CuLi$[e] | −50 → −25 °C | **3e** | ≥95:5 | *R*[f] | 75 |
| 6 | $(H_2C{=}CHCH_2)_2CuLi$[e] | −78 °C → RT[h] | **3f** | 89:11 | *S*[g] | 54 |

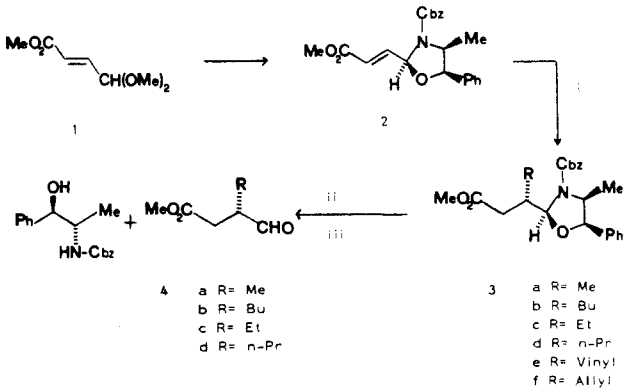
[a] **2** was prepared from dimethyl acetal 1 and *N*-(benzyloxycarbonyl) norephedrine as described in ref 3. All cuprate additions were performed in $Et_2O$ or in $Et_2O$/THF. All new compounds showed satisfactory elemental analysis. [b] Determined by $^{13}C$ and $^1H$ NMR spectroscopy. [c] Unless otherwise stated, the absolute configuration was determined by transforming products **3** into the corresponding aldehydes (see Table II). [d] Reaction was carried out as described in ref 2d. [e] $(H_2C{=}CH)_2CuLi$ and $(H_2C{=}CHCH_2)_2CuLi$ were generated by using the CuBr·$Me_2S$ complex. [f] Absolute configuration was determined by catalytic reduction (5% Rh–alumina) to **3c**. [g] **3f** was reduced (5% Rh–alumina) to **3d**, which was then transformed into the known aldehyde **4d**. [h] RT = room temperature.

**Table II. Synthesis of Aldehydes 4a–d[a]**

| entry | aldehyde | R | $[\alpha]_D$[b] (*c* 1, $Et_2O$) | % ee[c] | yield, % |
|---|---|---|---|---|---|
| 1 | **4a** | Me | −71.2° | 93[d] | 85 |
| 2 | **4b** | Bu | −68.5° | 91 | 80 |
| 3 | **4c** | Et | −69.8° | 90 | 84 |
| 4 | **4d** | *n*-Pr | −58.4° | 78 | 82 |

[a] Oxazolidines **3a–d** were treated overnight with ethanedithiol (10 mol equiv) in $CH_2Cl_2$ in the presence of $BF_3$·$Et_2O$ (0.5 mol equiv). The crude reaction mixtures were then refluxed under stirring for 10 h in a 4:1 acetone/$H_2O$ solution containing MeI (10 mol equiv) and $CaCO_3$ (3 equiv). [b] Literature values are reported in ref 5. [c] Enantiomeric excesses were estimated by 200-MHz $^1H$ NMR by using $Eu(hfc)_3$ as shift reagent. [d] Aldehyde **4a** was also reduced (LAH, $Et_2O$) to (2*S*)-2-methylbutanediol, $[\alpha]_D$−13.4° (*c* 0.7, MeOH) (lit. $[\alpha]_D$ − 14.4° (*c* 0.6, MeOH): Leuenberger, H. G. W.; Boguth, W.; Barner, R.; Schmid, M.; Zell, R. *Helv. Chim. Acta* **1979**, *62*, 455).

**Scheme I[a]**

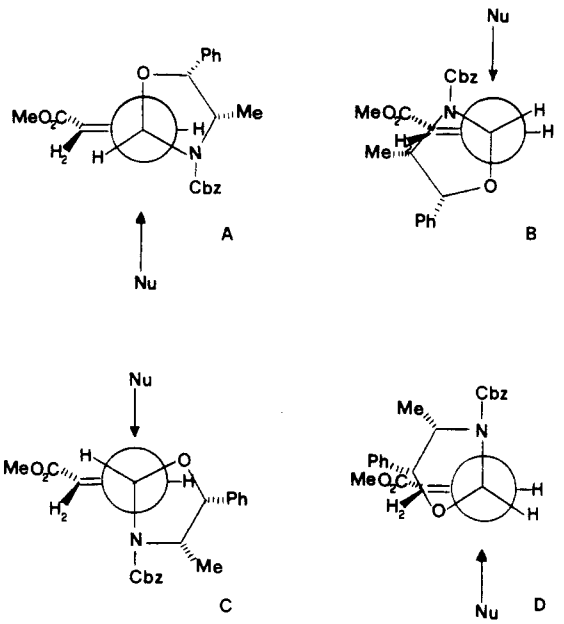



[a] Reagents: (i) $R_2CuLi$; (ii) $HSCH_2CH_2SH$, $BF_3$·$Et_2O$; (iii) MeI, $CaCO_3$, $H_2O$.

of both enantiomers of the title aldehydes. Cuprate addition occurs always from substrate *si* face, even in the case of the allylic cuprate (Table I, entry 6), which usually exhibits a diastereoface selection opposite to that of aliphatic and vinylic reagents.[8] The same kind of selectivity is also observed when the reaction is carried out in the presence of trimethylsilyl chloride (Table I, entry 2). As recently shown by Corey,[2d] under these conditions the d(Cu),$\pi$*-complex formation, which is usually a reversible equilibrating process, becomes irreversible, so that diastereoselectivity can be discussed in terms of $\pi$-face differentiation.

The stereochemical outcome of nucleophile additions to an $\alpha,\beta$-unsaturated carbonyl system have been interpreted

**Chart I**




in terms of models A–D (Chart I).[1,2] On the basis of MO considerations, we assume that transition structure models A and B are the most likely to be involved. In fact, in the MO formalism, the LUMO of the electrophile is favorably affected through the mixing of the $\pi$* orbital with the lowest energy $\sigma$* orbital, which is associated with the most electronegative substituent, e.g., the oxygen in Chart I.[9] For such an effect to operate, the electronegative substituent must occupy the perpendicular positions, as happens in A and B (Felkin–Anh-type models[9]).

Nucleophile–substrate steric interactions are not likely to be crucial in discriminating between these two transition structure models. Actually they could be expected to be determining if the nucleophile approached along the Bürgi–Dunitz trajectory (~109°),[9] and in this case, structure B (Nu–H interaction) rather than A (Nu–NCbz interaction) would be favored. This is not experimentally observed, and indeed, as cuprate reagents are d-nucleophiles[10] they need not follow such a trajectory in their approach to $\pi$-systems.[11] On the other hand, the energy difference between A and B could well arise from the different steric hindrance exerted on $H_2$ by the allylic substituents. Destabilization of B by $H_2$-ring interaction could determine preferential reaction through A, thus

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accounting for the observed selectivity.[12,13]

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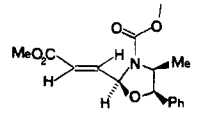
**Registry No.** 2, 105226-55-9; 3a, 105140-27-0; 3b, 105140-28-1; 3c, 105140-29-2; 3d, 105140-32-7; 3e, 105140-30-5; 3f, 105140-31-6; 4a, 105226-56-0; 4a (1,4-diol), 70423-38-0; 4b, 71633-61-9; 4c, 71464-83-0; 4d, 71464-84-1; $Bu_2CuLi$, 24406-16-4; $Me_2CuLi$, 15681-48-8; $Et_2CuLi$, 38297-20-0; $(CH_2{=}CH)_2CuLi$, 22903-99-7; $(CH_2{=}CHCH_2)_2CuLi$, 21500-57-2.

**Supplementary Material Available:** $^1H$ and $^{13}C$ NMR data for compounds **3a–f** and $^1H$ NMR data for ester **2** and for aldehydes **4a–d** (2 pages). Ordering information is given on any current masthead page.

(12) To assess this point we performed MM calculations on model compound **5** which, upon cuprate addition, shows the same stereoselectivity as **2**. It turned out that, at ground-state level, B-type conformer is disfavored over A-type by 1.5 kcal/mol.




5

(13) As pointed out by one of the referees, metal coordination phenomena, by either the allylic oxygen or the carbamate group could also be important in determining the stereochemical outcome. Further work is in progress to clarify this aspect.

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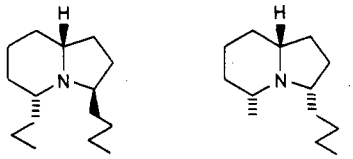
*Received June 2, 1986*

## A Short Total Synthesis of (±)-Gephyrotoxin-223AB

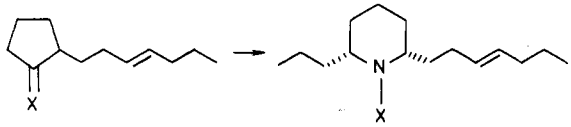
*Summary:* (±)-Gephyrotoxin-223AB has been synthesized from 2-carbomethoxycyclopentanone in nine steps by a route utilizing the stereoselective homolytic cyclization of an alkenyl-substituted *N*-chloropiperidine.

*Sir:* Recent years have witnessed a proliferation of synthetic strategies based upon the intramolecular cyclization reactions of carbon-centered radicals.[1] By contrast, the synthetic potential of nitrogen-centered radicals[2] has not been as frequently exploited. Surzur and Stella[3] have shown that metal-complexed aminyl radicals can be generated under mild conditions by treatment of the corresponding *N*-chloramines with a variety of reducing metal salts including titanium trichloride, iron(II) chloride, and copper(I) chloride (with or without added copper(II) chloride). The species so produced undergo intramolecular addition to double bonds in much the same manner as their carbon-centered radical counterparts. The facility of these cyclizations coupled with the ready availability of both *cis*- and *trans*-2,6-dialkylpiperidines[4] suggested to us the possibility of using aminyl radical heterocyclizations for the construction of indolizidine alkaloids such as gephyrotoxin-223AB (**1**)[5] and monomorine (**2**).[6] We now report a short stereoselective synthesis of gephyrotoxin-223AB,[7] a constituent of the skin extracts of neotropical poison-dart frogs (family Dendrobatidae).




1 2

Alkylation of the dianion of 3-butynol[8] with *n*-propyl bromide [*n*-PrBr (1.1 equiv), THF–HMPA (3:1), −78 → 20 °C, 6 h] generated 3-heptynol in 91% yield. Reduction of this material with sodium in liquid ammonia [1 h, $NH_4Cl$ quench] provided (*E*)-3-heptenol in 95% yield (stereohomogeneous by $^{13}C$ NMR). This alcohol was converted to its mesylate [MsCl (1.1 equiv), $NEt_3$, $CH_2Cl_2$, 0 °C, 1 h] in quantitative yield and the crude mesylate was used to alkylate the sodium enolate of 2-carbomethoxycyclopentanone[9] [toluene, reflux, 6 h]. Decarbomethoxylation[10] of the resulting crude β-keto ester [NaCN, $H_2O$, $Me_2SO$, 140 °C, 70 min] gave the (*E*)-alkenylcyclopentanone **3**[11] in 53% overall yield from 2-carbomethoxycyclopentanone.




3, X = O
4, X = NOH

5, X = H
6, X = Cl

Treatment of **3** with hydroxylamine hydrochloride and sodium acetate in methanol gave the anti oxime **4** (70%). Oxime **4** was then converted into the 2,6-cis-disubstituted piperidine **5** under the conditions defined by Yamamoto[4a] [(i) MsCl, $NEt_3$, $CH_2Cl_2$, −20 °C, 30 min; (ii) Al(*n*-Pr)$_3$ (3 equiv), $CH_2Cl_2$–toluene (7:2), −78 → 20 °C, 1 h; (iii) DIBAL (2 equiv), $CH_2Cl_2$, −78 °C/2 h, 0 °C/2 h]. Piperidine **5** was obtained in 41% yield after flash chromatography on silica

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(7) For other syntheses of 1, see: (a) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (c) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, 1515. For syntheses of stereoisomers of 1, see: (d) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103. (e) Hart, D. J.; Tsai, Y. M. *J. Org. Chem.* **1982**, *47*, 4403. For two more recent syntheses of 1 and a comprehensive review of work in this area, see: Daly, J. W.; Spande, Th. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1986; Vol. 4, p 1.
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(11) New compounds except **6**, **8**, and **10** were fully characterized by $^1H$ NMR, IR, and HRMS and/or microanalysis. The rather labile chloramines were characterized by $^1H$ and $^{13}C$ NMR. All were stereohomogeneous.

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